Remarks

Reconsideration of the application is respectfully requested in view of the following remarks. Claims 1-6, 8-53, and 61-67 remain in this application. New claims 68-70 have been added, and claims 7 and 54 have been canceled. No claims have been allowed. Claims 1, 29, 31, 33, 36, 47, 50, 61, 64, and 68 are independent.

Cited Art

The Action relies on Chen et al. "Ratio-Based Decisions and the Quantitative Analysis of cDNA Microarray Images," Journal of Biomedical Optics, 1997, vol. 2:364-373 ("Chen I"); Jain et al., IEEE Transactions on Pattern Analysis and Machine Intelligence, 2000, vol. 22:4-37 ("Jain"); and Chen et al., Proc. SPIE, 1999, vol. 3602:422-428 ("Chen II").

Examiner Interview

Applicants wish to thank the Examiner and Supervisor for their time during a personal interview with the undersigned attorney on December 9, 2003.

Background of Effectiveness and Relatedness

During the interview, the Examiner expressed skepticism regarding how a measurement of effectiveness of a model predicting gene expression could indicate relatedness of the genes for which gene data is used in the model. However, one of the innovations of the technology described in the patent application involves recognizing a connection between effectiveness and relatedness. For instance, a particular example at page 12, lines 27 et seq. of the Application describes that effectiveness of a model and the quantification of relatedness can be the same value:

> For the model 704, a value of 0.74 is provided and quantifies the effectiveness of the model 704 and the relatedness of the genes G_1, G_2, and G_3 (and the condition C_1). In the example, a high value indicates more relatedness than a low value, and the value falls between 0 and 1.

A subsequent section of the Application starting at page 28, line 12 describes how experimental results established that such a connection exists and can be employed in a useful way. Finally, as

described in the Application at page 4, lines 8-9, a technique for identifying related genes can be useful in identifying a group of genes as related for further investigation by researchers.

Patentability of Claims 1-54 and 61-65 under § 112, ¶ 1

The Action rejects claims 1-54 and 61-65 as containing subject matter not described in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention. Applicants respectfully disagree with the rejection for the reasons pointed out in earlier replies. However, in the interest of further expediting prosecution, Applicants present a number of amendments to clarify the claim language. Applicants reserve the right to pursue to original claims in a continuation application.

The language of claim 1 concerning relatedness and effectiveness is supported by the specification as required by § 112 ¶ 1. Claim 1 now recites in part:

> measuring effectiveness of the nonlinear model in accurately predicting gene expression of the predicted gene as compared to the gene expression level observations, the effectiveness being a quantification of relative gene relatedness of the predicted gene and the subset combination . . . with respect to other subset combinations of the candidate genes . . .

For example, at page 12, lines 17-21, the Application states:

> At FIG. 7B, a table 754 illustrates an exemplary measurement of the effectiveness of the model 704. Data collected during *k* microarray experiments is applied to the model 704, which produces a predicted value for G_3 for each experiment ($G_{3\ pred}$). In the example, effectiveness of the model 704 is calculated by comparing $G_{3\ pred}$ with G_3 observed across the data set comprising the experiments.

And, at page 12, lines 27 et seq., the Application states (emphasis added):

> For the model 704, a value of 0.74 is provided and *quantifies the effectiveness of the model 704 and the relatedness of the genes* G_1, G_2, and G_3 (and the condition C_1). In the example, a high value indicates more relatedness than a low value, and the value falls between 0 and 1.

The action 816 of FIG. 8 and other actions in the drawings and text provide further support. The Application as filed thus supports the claim amendments.

Although the Application does not use the exact phrase "relative relatedness," § 112 ¶ 1 does not require the words to appear *in haec verba* in the Application (*see*, MPEP § 2163.02); rather the language must reasonably convey to one of skill that the inventor had possession of the claimed subject matter at the time of filing. The Application's description of "a high value

indicates more relatedness than a low value" reasonably conveys that the Applicants were in possession of the claimed "relative relatedness" as recited by claim 1.

The remaining amendments to claim 1 are also supported by the specification. Without expounding at length on the support for the remaining amendments, Applicants point to examples where support can be found. For example, language reciting "subset combinations" has been substituted for "permutations." In support, the Application at page 18, line 15 describes "possible combinations of . . . predictive elements." Other language in the claim recites "indicating ranked relative gene relatedness." In support, the Application at FIG. 11 shows a screen capture indicating ranked relative gene relatedness.

Further, the claim now recites "inputs and . . . outputs." In support, the Application at page 13, lines 10-12 describes, "having the predictive elements as inputs and the predicted gene as an output."

For at least these reasons, claim 1 overcomes the new matter rejection under § 112 ¶ 1. Claims 31-32 do not include the terms "relatedness" or "effectiveness" and are therefore not at issue. Accordingly, claims 1-53 and 61-67 are allowable under § 112, ¶1.

Patentability of Claims 1-54 and 61-65 under § 112, ¶ 2

The actions of claim 1 as amended are sufficiently related, so claim 1 is not indefinite under § 112 ¶ 2. The Action has objected that it was unclear how the actions of the claim were related. Claim 1 now recites in part:

> A computer-implemented method for indicating ranked relative gene relatedness for a plurality of candidate genes . . . :
>
> For a predicted gene selected from the candidate genes . . . performing (a)-(c) . . .:
>
> (a) based on data comprising the plurality of gene expression level observations for the plurality of candidate genes, constructing a nonlinear model predicting gene expression for the predicted gene . . . ;
>
> (b) predicting gene expression of the predicted gene with the nonlinear model; and
>
> (c) measuring effectiveness of the nonlinear model in accurately predicting gene expression of the predicted gene as compared to the gene expression level observations, the effectiveness being a quantification of relative gene relatedness . . . ; and
>
> presenting a ranked plurality of the plurality of quantifications of relative relatedness for a plurality of the subset combinations of the candidate genes.

Applicants have thus amended the claim so that it is directed to an embodiment in which gene expression is predicted for a predicted gene (e.g., as described as in example in the Application at page 13, lines 10-12). The claim now weaves the language relating to the predicted gene throughout the claim so the actions are more clearly related.

The recitation of "effectiveness" is sufficiently clear, so claim 1 is not indefinite under § 112 ¶ 2. The Action comments that the application of effectiveness was unclear. The claim now recites "effectiveness of the nonlinear model in accurately predicting gene expression of the predicted gene." For example, the Application describes comparing a predicted value with an observed value. Elsewhere, at page 31, lines 11-12, the Application describes "Additions for further genes . . . do not increase the accuracy of the prediction."

Finally, Applicants have amended the claim to address the antecedent basis rejection identified in the Action. Applicants have removed the word "the" pointed out by the Action.

For at least these reasons, claim 1 now overcomes the § 112 ¶ 2 rejection.

The remaining claims also overcome the § 112 ¶ 2 rejection. For example, the Action points to claims 4 and 5, indicating positive limitations needed to be made to the claims. The claims have been amended to affirmatively recite additional method actions.

The Action also points to claims 7 and 10 as being in contradiction with the language of claim 1. Applicants see no such contradiction. Specifically, measuring effectiveness can comprise comparing without being in contradiction with effectiveness being a quantification of gene relatedness. In fact, in an example at page 12, lines 27 et seq., of the application, effectiveness and relatedness are described as being the same value.

The Action also points to claim 8, stating that constructing a model generally means to build something by concrete steps, which does not equate to choosing. Applicants point out that the Application describes constructing the model in software, and the software can choose a model. Therefore, constructing the model can comprise a choosing action.

The Action further points to claim 9 as unclear, alleging that the model's effectiveness cannot be determined by the model itself. However, the claim recites "evaluating the model," not that the model evaluates itself. Therefore, claim 9 is not indefinite.

The Action further points to claim 11 as lacking antecedent basis. Applicants have amended the claim accordingly.

The Action further points to claim 12 as unclear, inquiring how effectiveness can equate to quantification of gene relatedness. As described in the application, effectiveness can indeed be used as a quantification of relatedness. For example, in the example described at page 12, lines 27 et seq. of the application, effectiveness and relatedness are described as possibly being the same value. Therefore, the claim is not indefinite.

The Action points to claim 14 as circular. Again, Applicants point to the example described at page 12, lines 27 et seq. of the application, in which it is shown that effectiveness and relatedness can be the same value.

The Action also points to claim 15, stating that it fails to describe how a contribution is determined. Applicants have added language supported by page 17, lines 11-21 of the Application. The claim now overcomes the rejection.

Claims 31-32 do not include the terms "relatedness" or "effectiveness" and are therefore not at issue.

For at least these reasons, claims 1-53 and 61-67 are allowable under § 112, ¶2.

Patentability of Claims 29 and 30 over Chen I under § 102

The Action rejects claims 29 and 30 under 35 U.S.C. § 102 (b) as unpatentable over Chen I. Applicants respectfully submit the claims in their present form are allowable over the cited art. Chen I relates to the quantitative analysis of cDNA Microarray images, and technology related to the article was acknowledged in the Application at page 9, lines 6-8 and page 10, lines 19-21.

Claim 29 recites in part:

> ranking the groups of genes other than the target gene by coefficient of determination . . .

For example, the Application shows a ranking of genes in FIG. 11. The Action relies on Chen I as anticipating the recited arrangement, but Applicants respectfully disagree.

Table 1 and Chen I's accompanying discussion of confidence intervals does not anticipate "ranking the groups of genes other than the target gene by coefficient of determination." At page 371, Chen I shows Table 1 with the following heading:

> Table 1 Lower and upper limits at 95% confidence level, and other statistics of ratio density. Output distribution parameters, Input distribution [Coefficient of Variation] (c), lower limit, upper limit, mean, deviation, [coefficient of variation], peak.

In the accompanying text, Chen I describes:

> Table 1 lists the upper (right) limit and lower (left) limit of 95% confidence intervals for different *c* values, as well as the mean and standard deviation of the corresponding distributions.

Thus, Chen does describe a "coefficient of variation." However, the coefficient of variation is not described as related to a coefficient of determination, and Table 1 does not rank groups of genes as recited by claim 29.

Using Chen I's coefficient of variation in place of the Application's "coefficient of determination" would result in an inoperable combination. Starting at page 364, column 1, Chen I states (emphasis added):

> *Assuming* sample expression levels are independent, levels are normally distributed, and *there is a constant coefficient of variation for the entire gene set* (a biochemical consequence of the mechanics of transcript production), we derive the probability density of the ration, find the maximum-likelihood estimator for the distribution, and develop an iterative procedure for signal calibration.

So, Chen assumes a constant coefficient of variation for the entire gene set. By contrast, claim 29 recites "ranking the groups of genes other than the target gene by coefficient of determination." If the coefficient of determination were constant for all genes, ranking would be meaningless.

Accordingly, Chen I's disclosure does not anticipate claim 29. For at least these reasons, claim 29 and its dependent claim, 30, are allowable over the cited art.

Patentability of Claims 33-35 over Chen I, Chen II, and Jain under § 103

The Action rejects claims 33-35 under 35 U.S.C. § 103 (a) as unpatentable over Chen I, Chen II, and Jain. Applicants respectfully submit the claims in their present form are allowable over the cited art. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP § 2142.) In the present case, there is nothing within the references

themselves that would lead to a modification that would result in the claimed arrangement, and the references fail to teach or suggest all the claim limitations.

Chen II's description of K-mean clustering is insufficient to teach or suggest modification of the other two references to result in "testing effectiveness of the artificial intelligence function in predicting expression of the predicted gene to rate relative relatedness" as recited by claim 33; so the references in combination do not teach or suggest claim 33. Claim 33 recites in part:

> testing effectiveness of the artificial intelligence function in predicting expression of the predicted gene to rate relative relatedness of the predicted gene and at least one gene associated with the predictive elements.

The Action rejects claim 33, based on a Chen I-Chen II- Jain combination. In its abstract, Chen II describes:

> We propose a K-mean based algorithm in which gene expression levels fluctuate in parallel will be clustered together. The resulting cluster suggests some functional relationships between the genes, . . .

Thus, Chen II does describe "suggests some functional relationships between the genes." However, Chen II and the other references fail to describe that relatedness could be rated via testing effectiveness of an artificial intelligence function in predicting expression. For example, Chen II does not describe testing the effectiveness of the K-mean algorithm as a way of determining relatedness.

Jain's broad statements concerning biology and data mining are not sufficient to motivate one to combine the references in a way that would result in the claimed combination. In column 1, Jain states "Automatic (machine) recognition, description, classification, and grouping of patterns are important problems in . . . biology . . . " and "These applications include data mining . . . , and biometrics . . ." However, these bare statements are insufficient suggestion or motivation for one to test effectivness of an artificial intelligence function in predicting gene expression to rate relative relatedness. Broad conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence' [of obviousness]. See *In re Dembiczak,* 175 F.3d 1994 (Fed. Cir. 1999). Biology and data mining are broad fields of study, and a statement describing applying a general technology to the fields is not detailed enough to be a suggestion or motivation to use the references in such a way to result in the arrangement of claim 33.

Finally, Applicants have added language to the claim describing "presenting the relative relatedness." The three references do not teach or suggest, alone or in combination, the recited "presenting."

Accordingly, claim 33 and its dependent claims, 34-35, are allowable over a Chen I-Chen II-Jain combination.

Patentability of New Claims 68-70

To further focus the Application, Applicants have added new claims 68-70, which find support, for example at passages starting at page 18, line 14 and FIG. 25. These claims each recite patentably distinct subject matter not taught or suggested by the cited art.

For at least these reasons, claims 68-70 are allowable at this time.

Request for Interview

If any issues remain, the Examiner is formally requested to contact the undersigned attorney prior to issuance of the next Office Action in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. Applicants submit the foregoing formal Amendment so that the Examiner may fully evaluate Applicants' position, thereby enabling the interview to be more focused.

This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Conclusion

The claims in their present form should now be allowable. Such action is respectfully requested.

Respectfully submitted,

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